# Renal Denervation : From simplicity 1 to symplicity III what we have learned?

By
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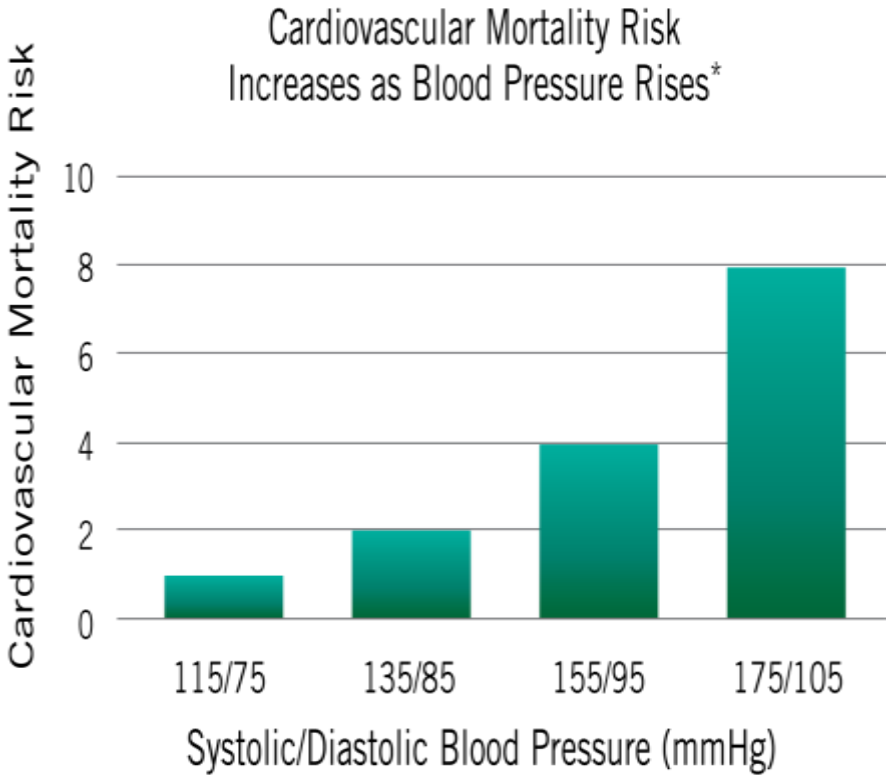
Mansoura University

- Hypertension remains a major global public health burden.
- An estimated 30–40% of the adult population in the developed world suffer from this condition.
- Every 20/10 mmHg increase in BP correlates with a doubling of 10-year cardiovascular mortality
- Only half of all treated hypertensives are controlled to established BP targets

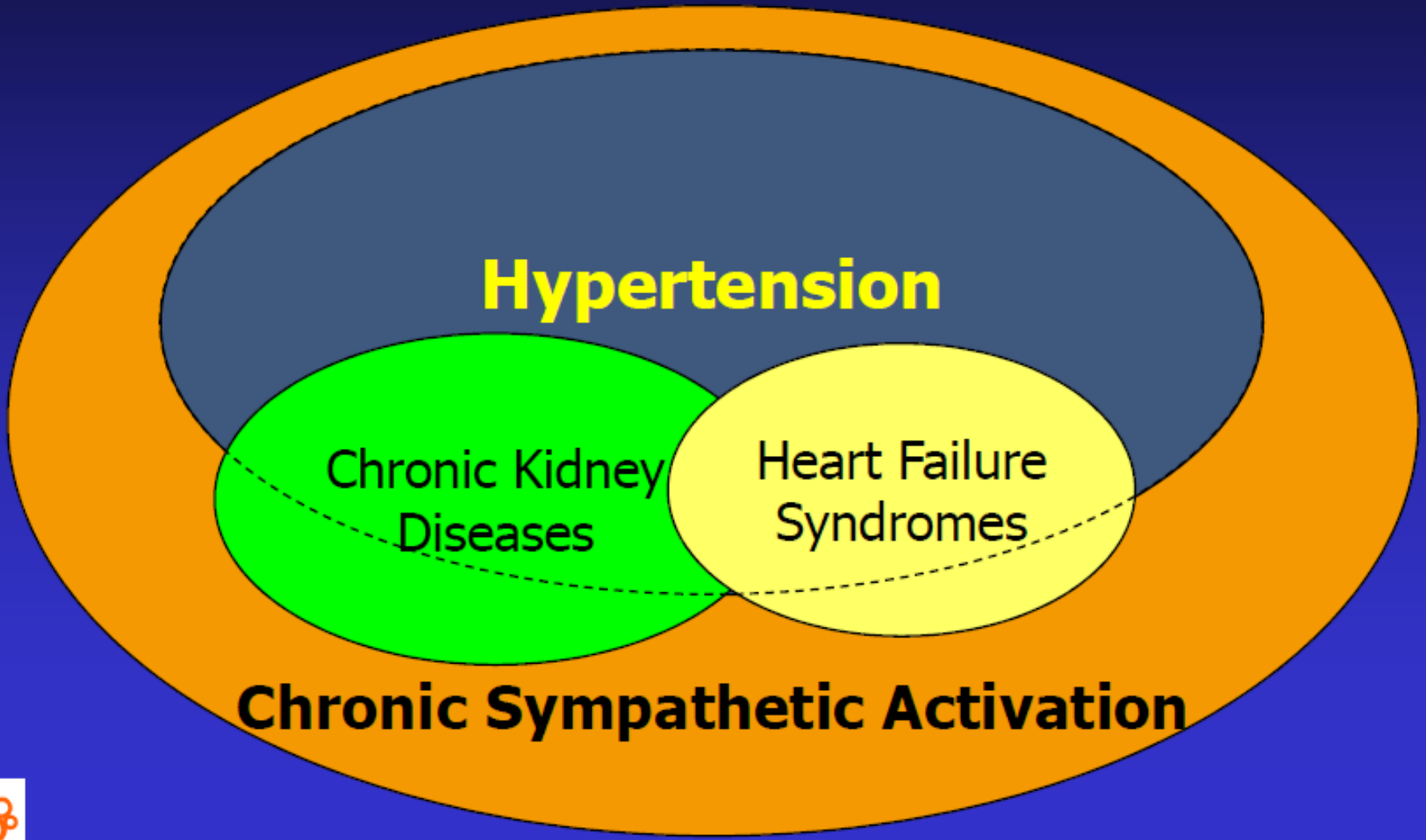



Lewington et al. 2002[2]

- 10% of patients with diagnosed hypertension have resistant hypertension(a systolic blood pressure of 140 mm Hg or higher despite adherence to at least three maximally tolerated doses of antihypertensive medications from complementary classes, including a diuretic at an appropriate dose) .

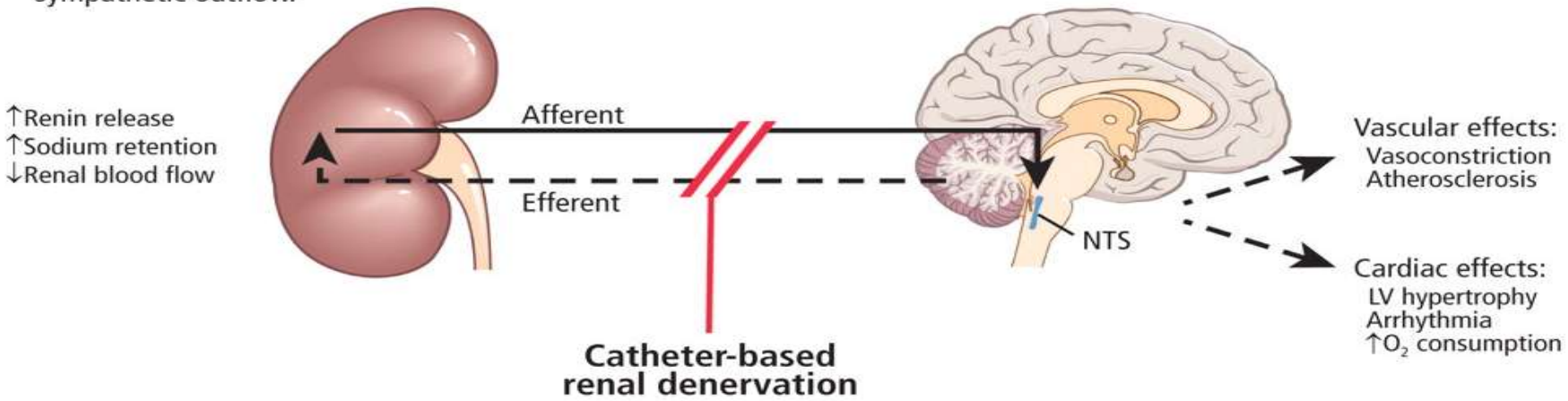
Sarafidis PA, Bakris GL. *J Am Coll Cardiol*. 2008.

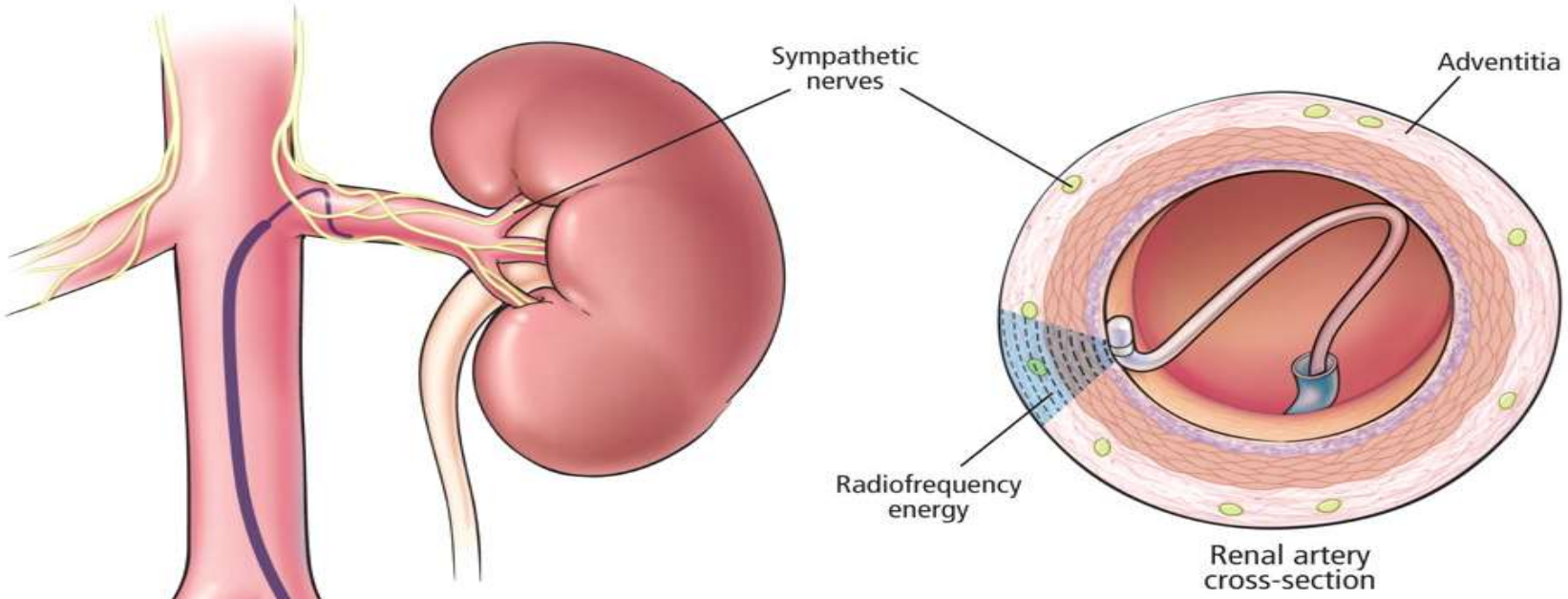
# Interrelationship of Heart & Kidney Disease



Kidneys, in response to ischemia, send afferent sympathetic signals to the brain that disinhibit the nuclei tractus solitarii (NTS), increasing sympathetic outflow.

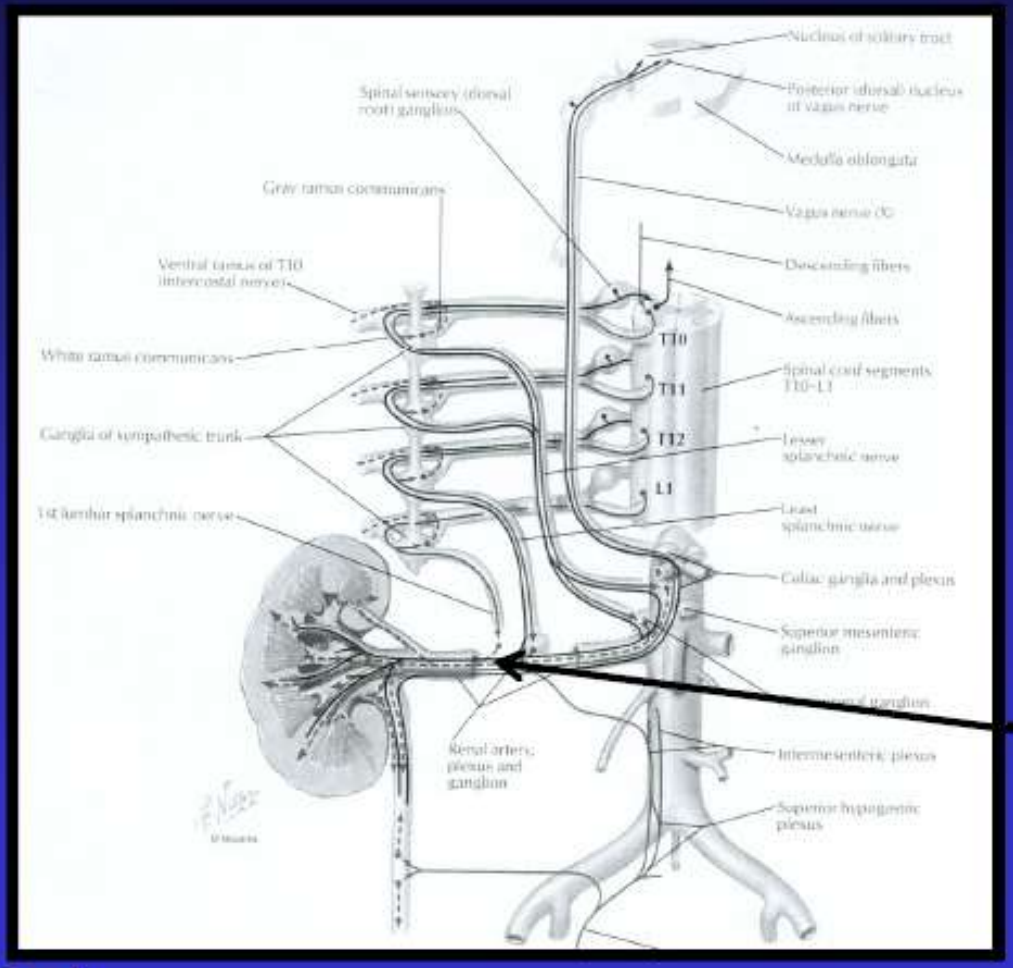
The NTS in the brainstem control efferent sympathetic signals from the brain to various organs of the body. Sympathetic signals raise blood pressure by increasing the heart rate, constricting arteries, and, in the kidney, increasing renin release and sodium and fluid retention.



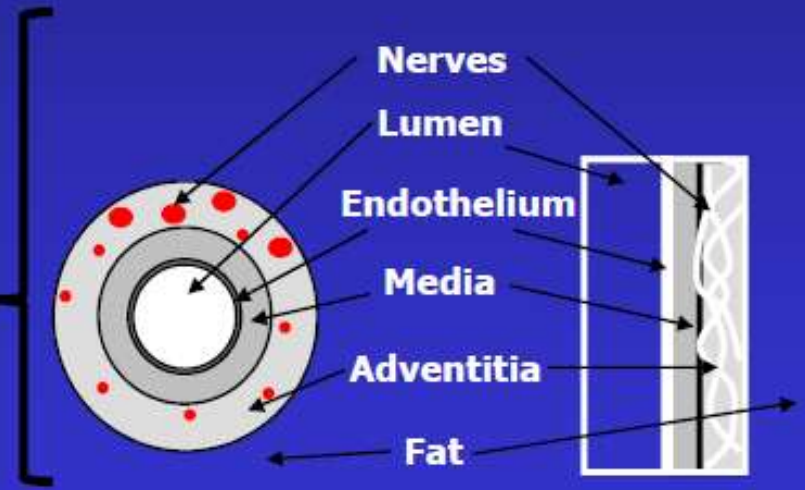




In the renal denervation procedure, a specially designed catheter is positioned in the renal artery, and radiofrequency energy is applied to the endoluminal surface.

# Renal Sympathetics as Denervation Target




- Arise from T10-L1
- Follow the renal artery to the kidney
- Primarily lie within the adventitia



# Surgical History

THE EFFECTS OF PROGRESSIVE SYMPATHECTOMY ON BLOOD PRESSURE

BRADFORD CANNON

*From the Laboratories of Physiology in the Harvard Medical School*

Received for publication March 24, 1931

Dr. Reginald H. Smithwick

THE EFFECT OF RENAL DENERVATION ON THE LEVEL OF ARTERIAL BLOOD PRESSURE AND RENAL FUNCTION IN ESSENTIAL HYPERTENSION

By IRVINE H. PAGE and GEORGE J. HEUER

*(From the Hospital of the Rockefeller Institute for Medical Research, New York, and the Department of Surgery, New York Hospital, New York)*

(Received for publication September 12, 1934)

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VOL. 152, NO. 16 — CHICAGO, ILLINOIS — AUGUST 15, 1953

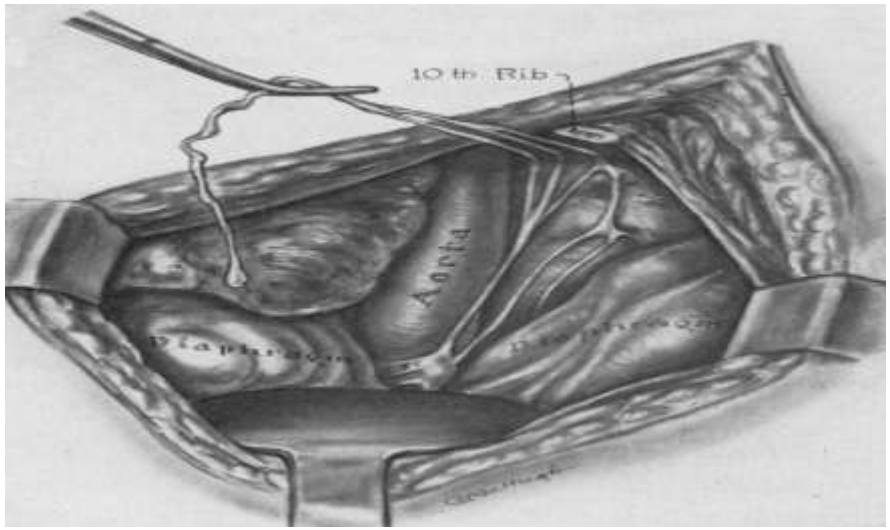


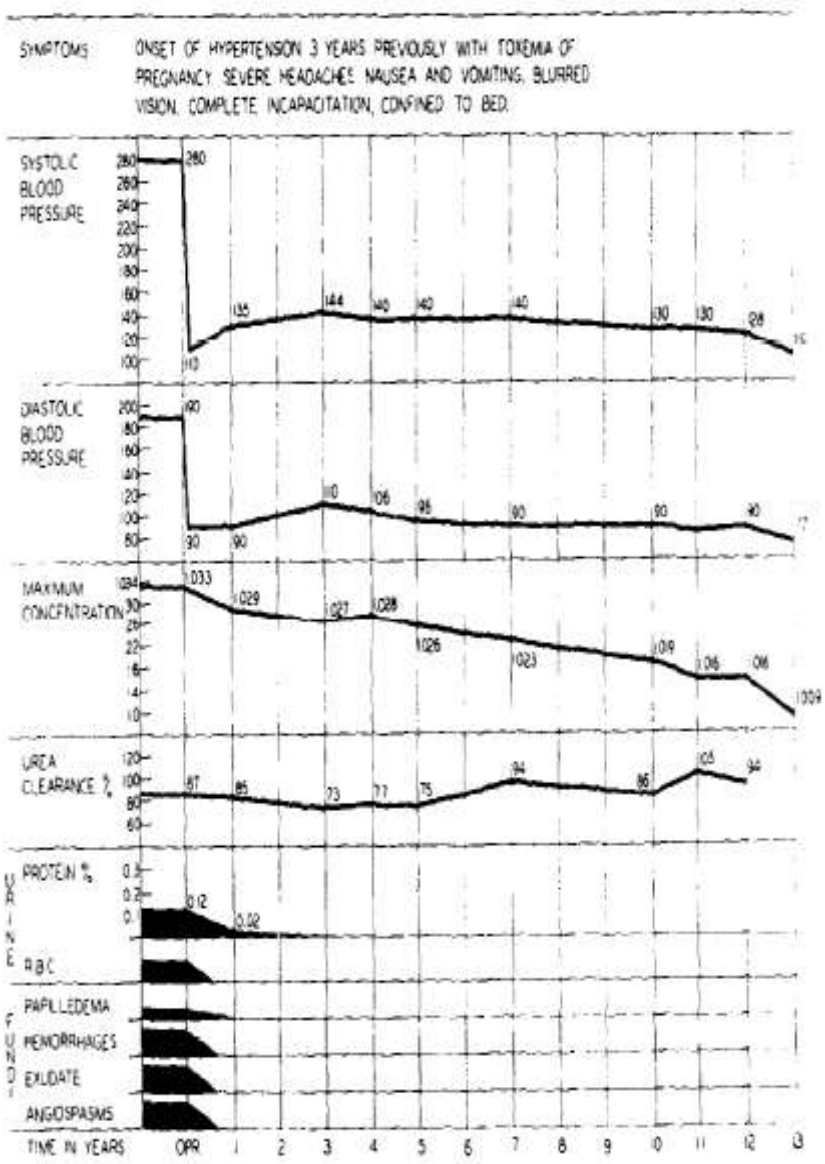
SPLANCHNICECTOMY FOR ESSENTIAL HYPERTENSION

RESULTS IN 1,266 CASES

*Reginald H. Smithwick, M.D.*
*and*
*Jesse E. Thompson, M.D., Boston*

# Surgical Sympathectomy

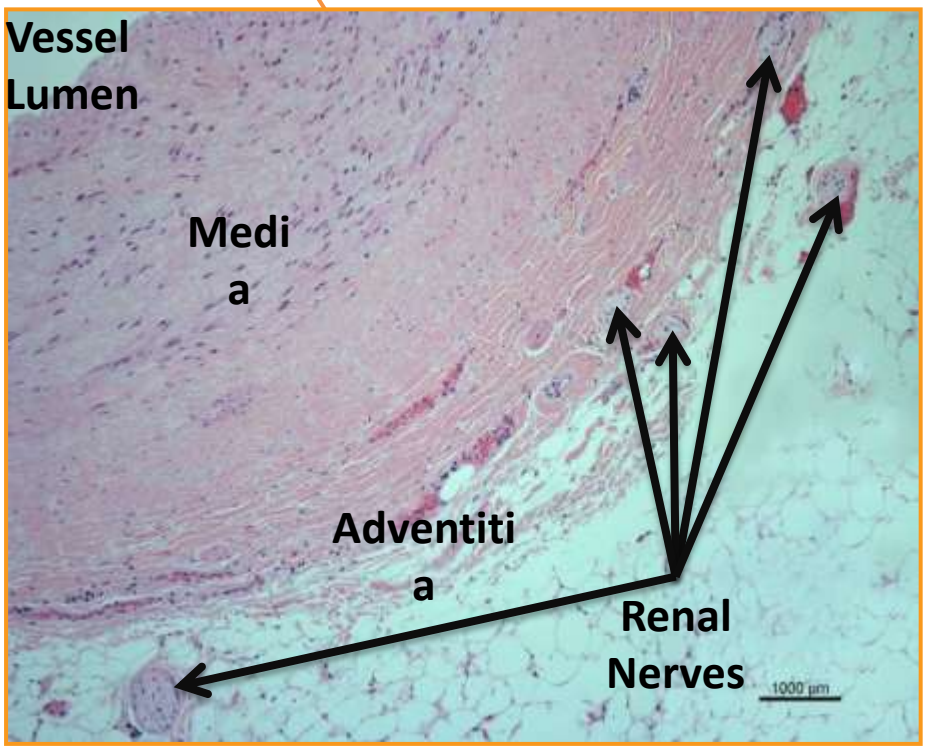



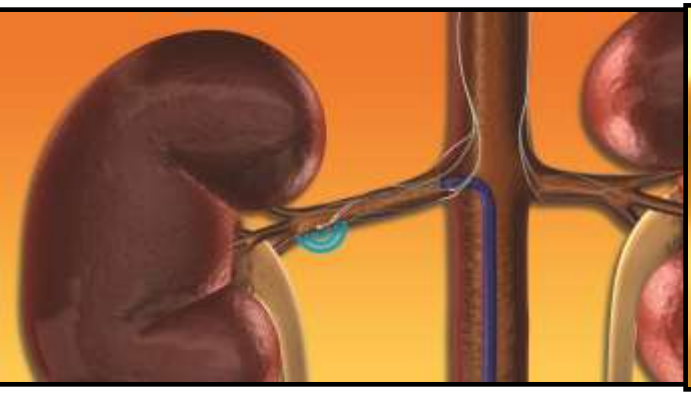

Grimson, Ann Surg 1941

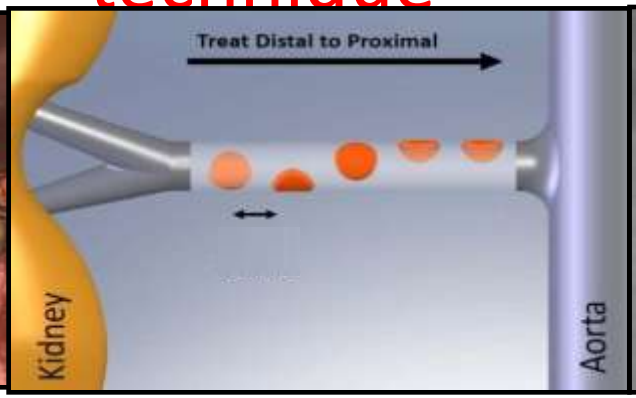
- The Symplicity system is the name of a series of trials sponsored by the Medtronic company that are evaluating the efficacy and safety of therapy with a renal denervation catheter for a variety of problems, but most importantly for hypertension.

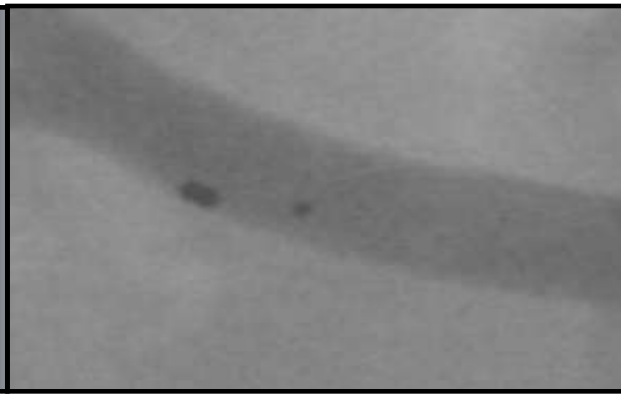
- launched in Europe in 2010 and is also currently available in Asia, Africa, Australia, and Canada. No renal denervation system has yet been approved in the United States.



# Catheter-Based Approach technique

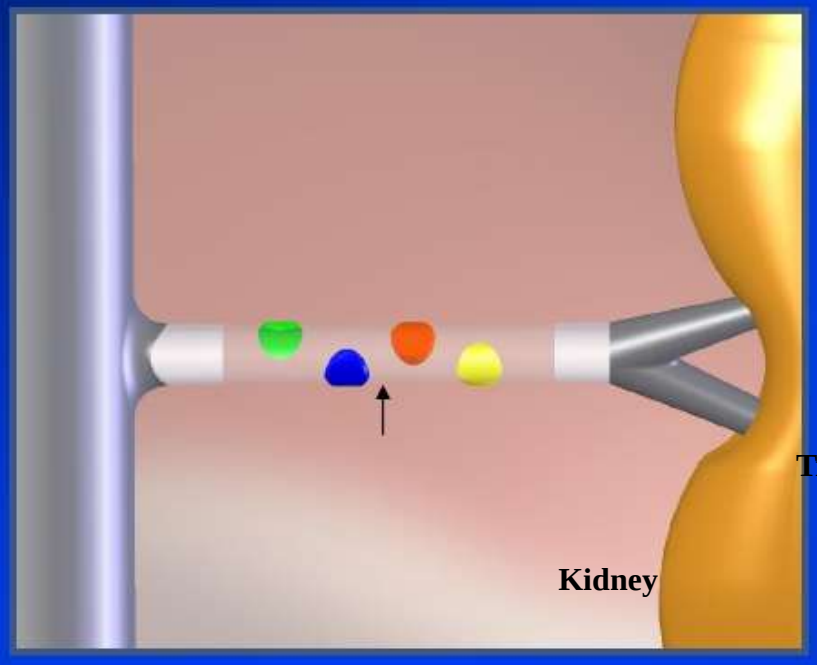




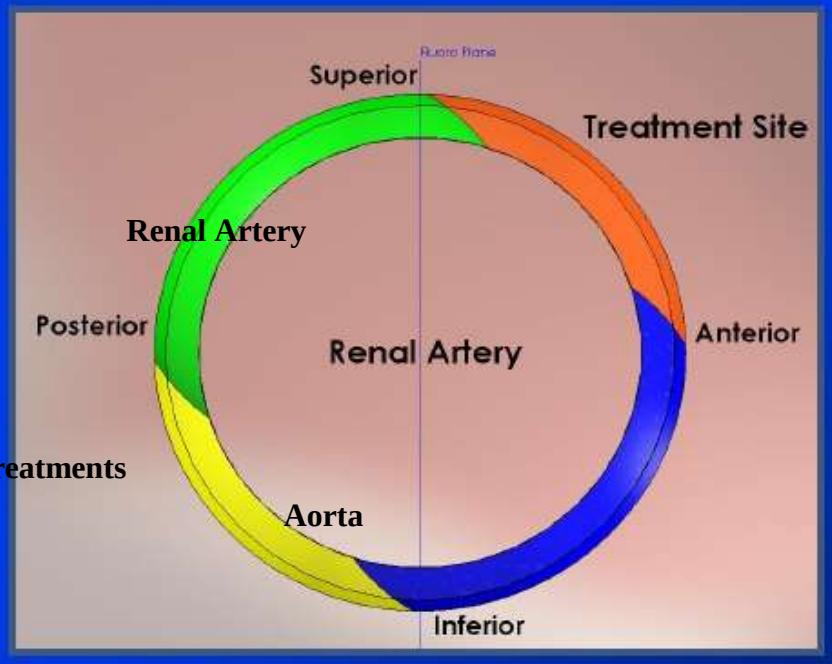
- Renal artery access via standard interventional
- 4-6 two-minute treatments per artery
- Proprietary RF generator
- Automated
- Low power (Released Energy maximum 8 Watt)
- Built-in safety algorithms
- Temperature between 40-75 °
- The generator automatically switch of if
- Temperature is higher than 75 °
- Five renal denervation catheter systems have already

# Treatment Strategy




Focal ablations

spaced along vessel




Treatments

Multiple focal ablations

↑ circumferential coverage

# Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study

*Henry Krum, Markus Schlaich, Rob Whitbourn, Paul A Sobotka, Jerzy Sadowski, Krzysztof Bartus, Boguslaw Kapelak, Anthony Walton, Horst Sievert, Suku Thambar, William T Abraham, Murray Esler*

## Summary

**Background** Renal sympathetic hyperactivity is associated with hypertension and its progression, chronic kidney disease, and heart failure. We did a proof-of-principle trial of therapeutic renal sympathetic denervation in patients with resistant hypertension (ie, systolic blood pressure ≥160 mm Hg on three or more antihypertensive medications, including a diuretic) to assess safety and blood-pressure reduction effectiveness.

**Methods** We enrolled 50 patients at five Australian and European centres; 5 patients were excluded for anatomical reasons (mainly on the basis of dual renal artery systems). Patients received percutaneous radiofrequency catheter-based treatment between June, 2007, and November, 2008, with subsequent follow-up to 1 year. We assessed the effectiveness of renal sympathetic denervation with renal noradrenaline spillover in a subgroup of patients. Primary endpoints were office blood pressure and safety data before and at 1, 3, 6, 9, and 12 months after procedure. Renal angiography was done before, immediately after, and 14–30 days after procedure, and magnetic resonance angiogram 6 months after procedure. We assessed blood-pressure lowering effectiveness by repeated measures ANOVA. This study is registered in Australia and Europe with ClinicalTrials.gov, numbers NCT 00483808 and NCT 00664638.

**Findings** In treated patients, baseline mean office blood pressure was 177/101 mm Hg (SD 20/15), (mean 4·7 antihypertensive medications); estimated glomerular filtration rate was 81 mL/min/1·73m² (SD 23); and mean reduction in renal noradrenaline spillover was 47% (95% CI 28–65%). Office blood pressures after procedure were reduced by −14/−10, −21/−10, −22/−11, −24/−11, and −27/−17 mm Hg at 1, 3, 6, 9, and 12 months, respectively. In the five non-treated patients, mean rise in office blood pressure was +3/−2, +2/+3, +14/+9, and +26/+17 mm Hg at 1, 3, 6, and 9 months, respectively. One intraprocedural renal artery dissection occurred before radiofrequency energy delivery, without further sequelae. There were no other renovascular complications.

**Interpretation** Catheter-based renal denervation causes substantial and sustained blood-pressure reduction, without serious adverse events, in patients with resistant hypertension. Prospective randomised clinical trials are needed to investigate the usefulness of this procedure in the management of this condition.

**Funding** Ardian Inc.

*Lancet* 2009; 373: 1275–81
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March 30, 2009
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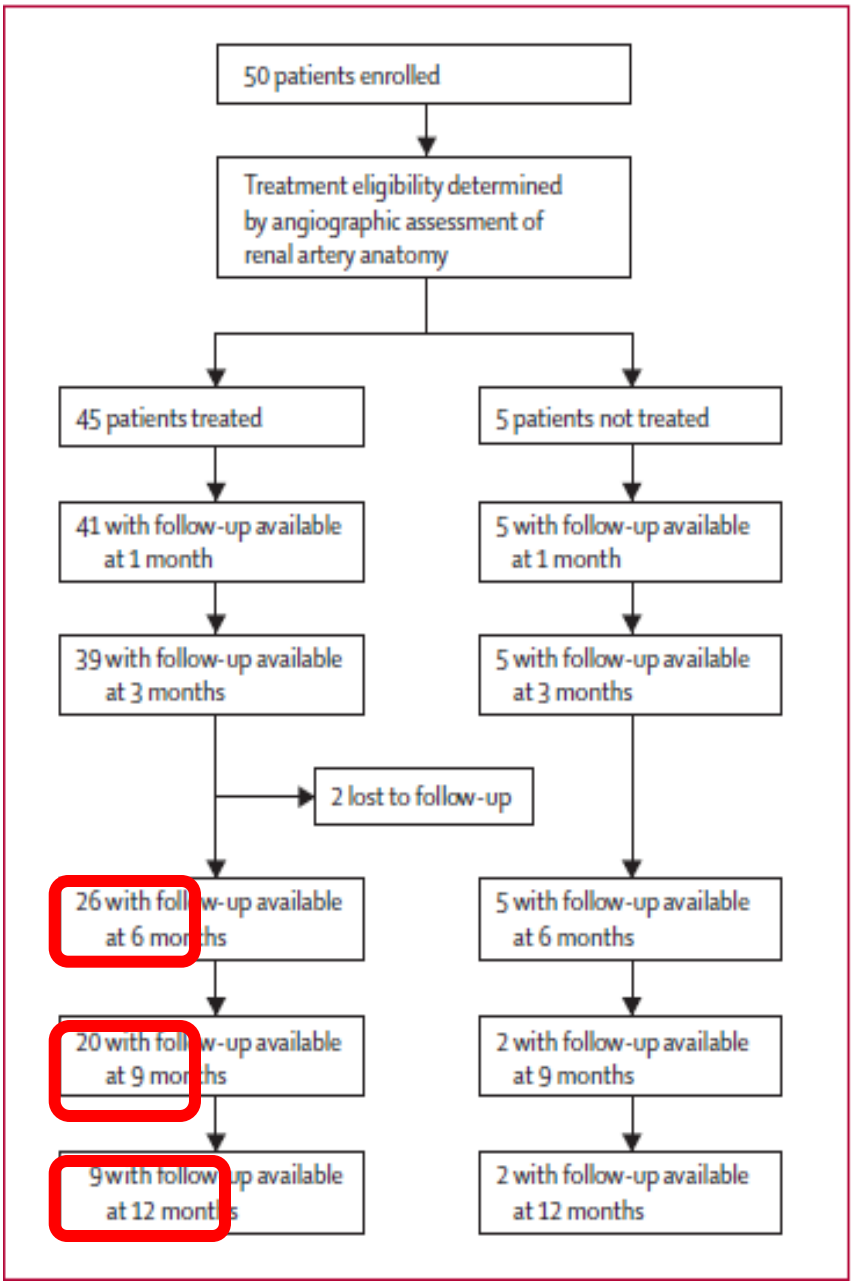
See Comment page 1228

**Centre of Cardiovascular Research and Education in Therapeutics, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, VIC, Australia** (Prof H Krum PhD); **Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia** (M Schlaich MD, Prof M Esler MBBS); **St Vincent's Hospital, Melbourne, VIC, Australia** (R Whitbourn MBBS); **Ardian Inc, Palo Alto, CA, USA** (P A Sobotka MD); **The Ohio State University, Columbus, OH, USA** (P A Sobotka, Prof W T Abraham MD); **Jagiellonian University, Krakow, Poland** (Prof J Sadowski MD, K Bartus MD, B Kapelak MD); **Alfred Hospital, Melbourne, VIC, Australia** (A Walton MBBS, Prof H Krum); **Cardiovascular Centre Frankfurt, Frankfurt, Germany** (Prof H Sievert MD); **and John Hunter Hospital, Newcastle, NSW, Australia**

# Trial profile

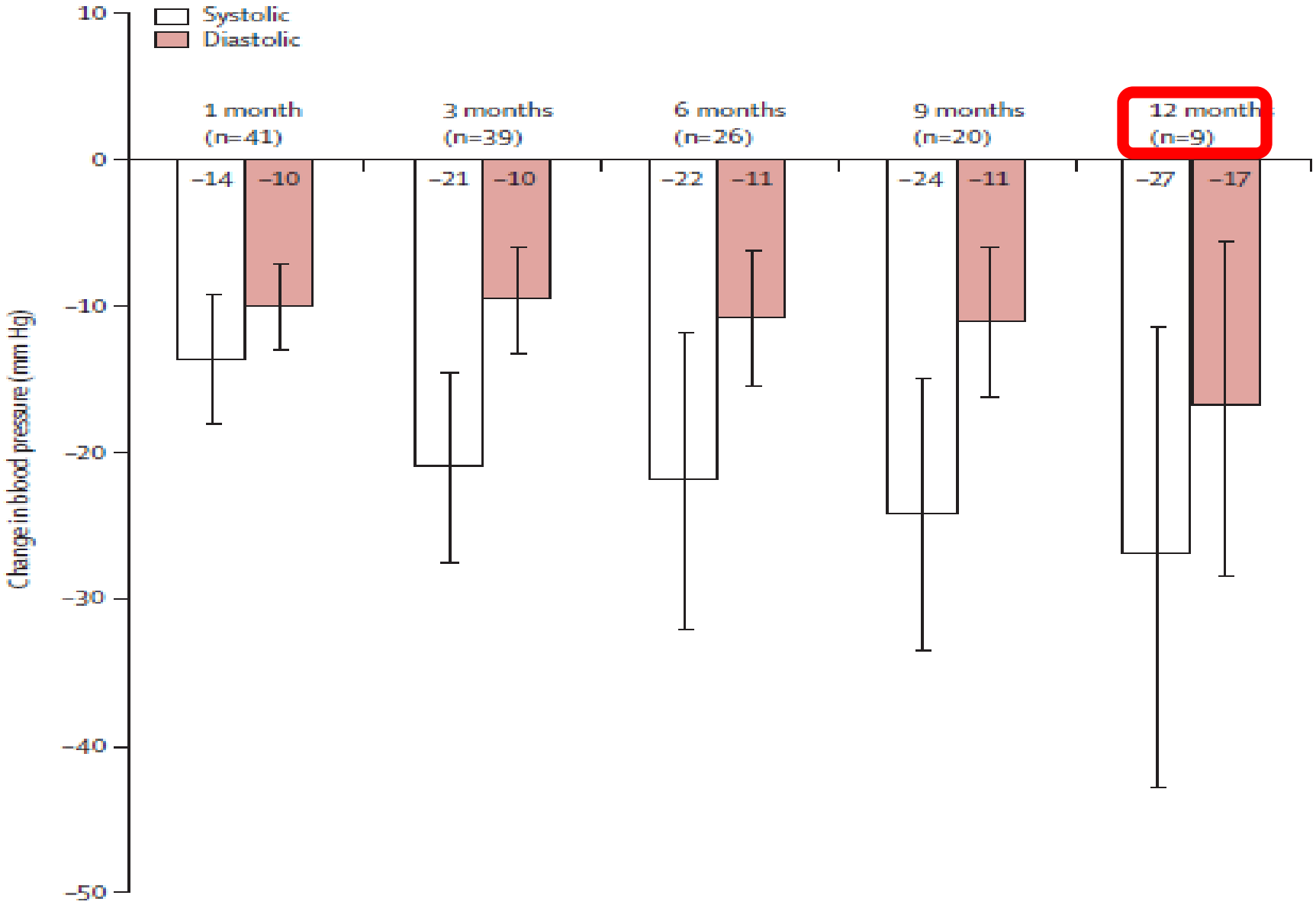



# Baseline patient characteristics

| | All patients (N=50) | Patients undergoing procedure (N=45) | Patients not eligible for procedure (N=5) |
|---|---|---|---|
| Age (years) | 57 (9) | 58 (9) | 51 (8) |
| Sex (female) | 21 (42%) | 20 (44%) | 1 (20%) |
| Ethnic origin (non-white) | 2 (4%) | 2 (4%) | 0 |
| Type 2 diabetes mellitus | 16 (32%) | 14 (31%) | 2 (40%) |
| CAD | 11 (22%) | 10 (22%) | 1 (20%) |
| Hyperlipidaemia | 34 (68%) | 29 (64%) | 5 (100%) |
| eGFR (mL/min/1·73 m²) | 83 (22) | 81 (23) | 95 (15) |
| Heart rate (bpm) | 73 (11) | 72 (11) | 79 (9) |
| Blood pressure (mm Hg) | 177/100 (19/14) | 177/101 (20/15) | 173/98 (8/9) |
| Number of antihypertension drugs | 4·7 (1·4) | 4·7 (1·5) | 4·6 (0·5) |
| ACE or ARB | 47 (94%) | 43 (96%) | 4 (80%) |
| β blocker | 39 (78%) | 34 (76%) | 5 (100%) |
| Calcium-channel blocker | 36 (72%) | 31 (69%) | 5 (100%) |
| Vasodilator | 8 (16%) | 8 (18%) | 0% |
| Diuretic | 46 (92%) | 43 (96%) | 3 (60%) |

Data are mean (SD) or number (%). ACE=angiotensin-converting enzyme inhibitor. ARB=angiotensin II receptor blocker. bpm=beats per minute. CAD=coronary artery disease. eGFR=estimated glomerular filtration rate.

# Change in office blood pressure



- **Non-response :**
- Six of 45 treated patients (13%) .

( had systolic blood-pressure reductions of less than 10 mm Hg) .

- **Changes in renal noradrenaline spillover :**
- Ten patients .
- The mean reduction in the was 47%.
- These same patients had a mean 6-month office blood-pressure reduction of 22/12 mm Hg, which was similar to the overall treatment cohort.
- **GFR (in 25 patients) :**
- Paired baseline and 6-month follow-up glomerular filtration rate data were available, and were 79 and 83 mL/min/1・73m2 .
- Six of 25 patients (24%) of patients had 20% or more improvement in glomerular filtration rate after the procedure.
- **Safety:**
- Diffuse visceral non-radiating abdominal pain
- Renal artery dissection: 1 patient .
- Pseudoaneurysm at the femoral access site : 1 patient.

Hypertension
Celebrating 30 Years: 1979 to 2009
JOURNAL OF THE AMERICAN HEART ASSOCIATION

# Catheter-Based Renal Sympathetic Denervation for Resistant Hypertension

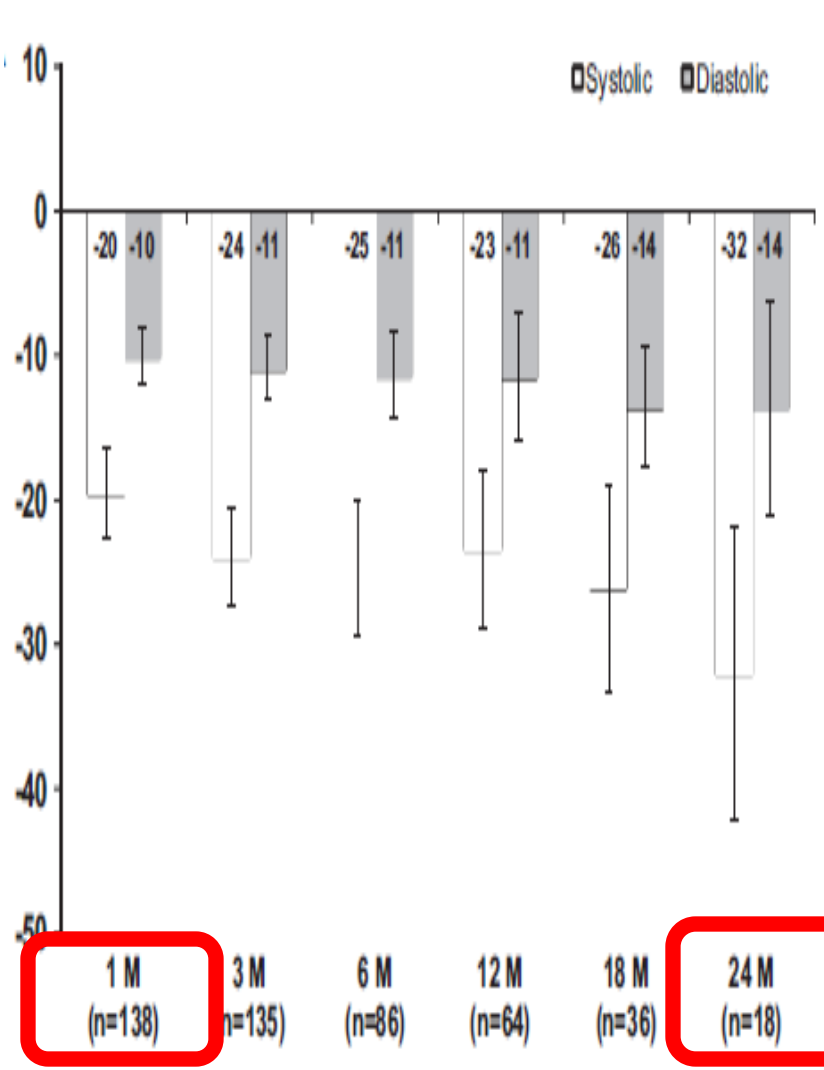
## Durability of Blood Pressure Reduction Out to 24 Months

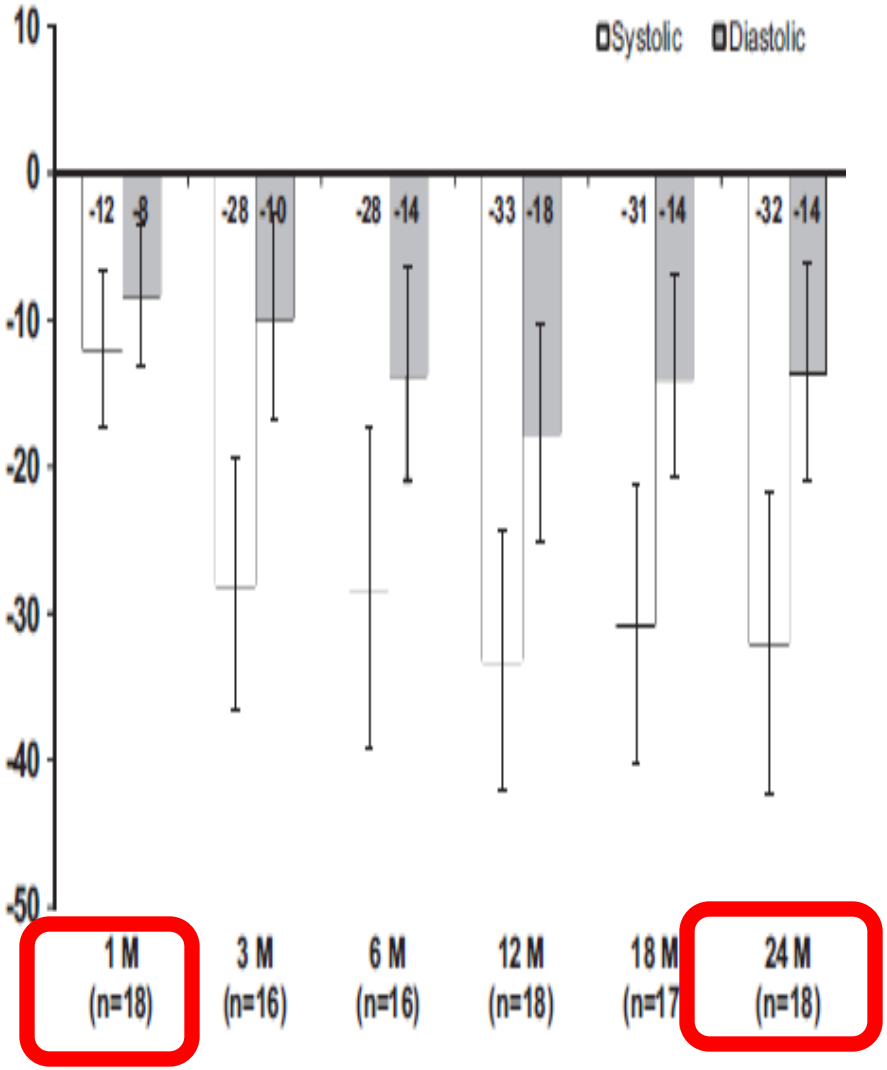
Symplicity HTN-1 Investigators*

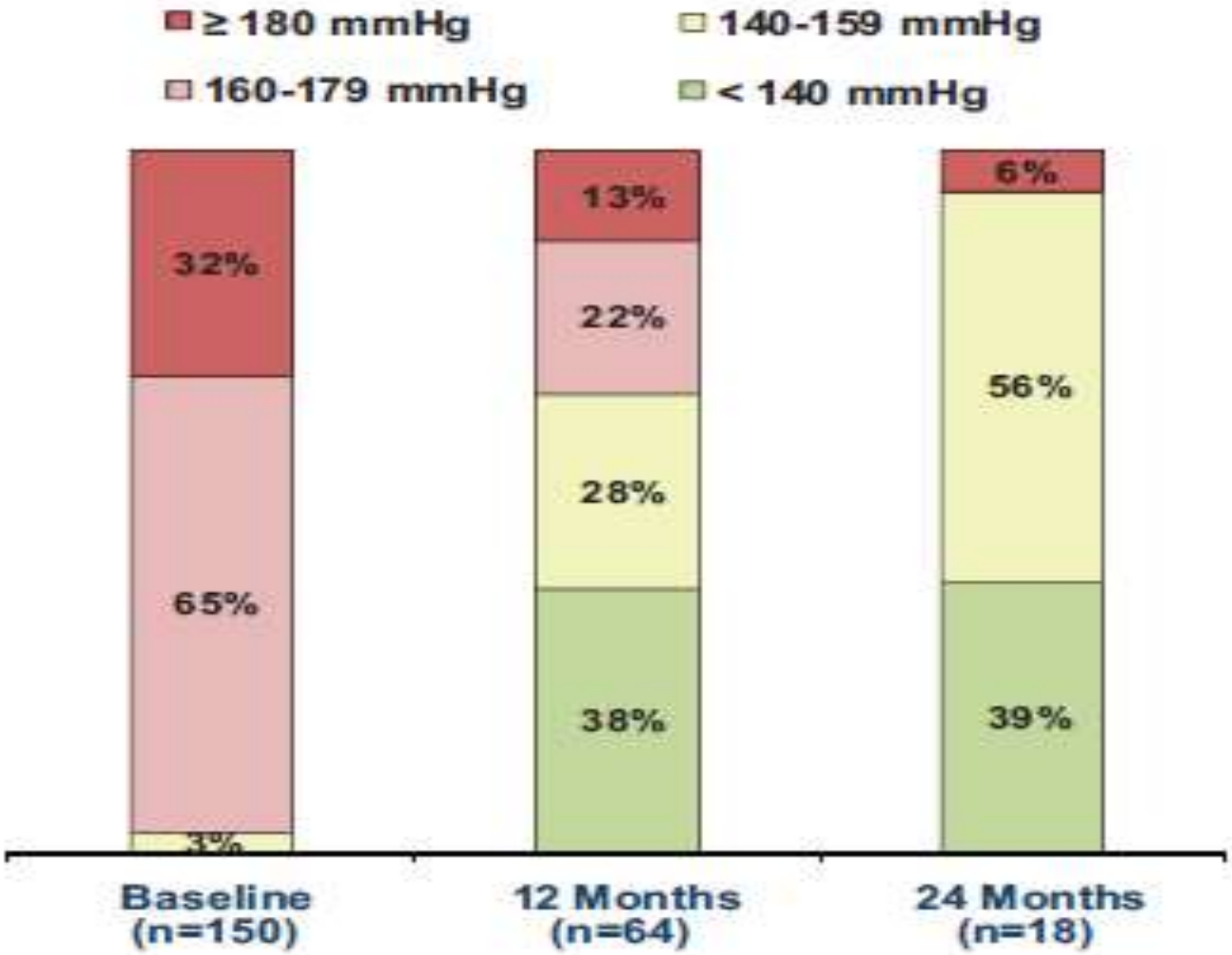
*Hypertension*. 2011;57:911-917.

**Systolic and diastolic changes where *P0.002) at all time points postprocedure with BPs* reduced on average by 20/10, 24/11, 25/11, 23/11, 26/14, and 32/14 mm Hg at 1, 3, 6, 12, 18, and 24 months**

**18 patients who had data out to 2 years there was, again, little change in BP values compared with the uncensored values.**




≥ 180 mmHg
140-159 mmHg
160-179 mmHg
< 140 mmHg
32%
65%
3%
13%
22%
28%
38%
6%
56%
39%
Baseline (n=150)
12 Months (n=64)
24 Months (n=18)

# *Baseline Predictors of BP Response*

- **Predictors of greater systolic BP response:**
- **Higher baseline systolic BP (*P0.0001) and use of central sympatholytic agents (P0.018).***
- **GFR:**
- **During the first year of follow-up, eGFR remained stable, with a change at 1, 3, 6, and 12 months of 0.1 mL/min -1.6 mL/min - 0.1 mL/min and 2.9 mL/min respectively.**
- **eGFR data were only available on 10 patients at 2 years. In these 10 patients, eGFR changed by - 16.0 mL/min per 1.73 m2 at 24 months postprocedure.**
- **In no cases did serum creatinine double, the patient develop class IV chronic kidney disease (15 to 29 mL/min per 1.73 m2), or the patient require dialysis.**
- ***Death***
- **Two patients died within the follow-up period postprocedure.**
- **Neither death was considered to be related to the device or the procedure.**

# Conclusion

- The initial reported BP reduction out to 12 months postrenal sympathetic denervation procedure has now been observed to persist out to 24 months of follow-up postprocedure.
- Elevated BP and use of central sympatholytics were predictors.
- The magnitude of BP lowering postprocedure at 24 months is no less than and appears to be numerically greater than that observed at 12 months.
- Hypthesis ??????:
- 1- A predominant procedure with a resetting of central sympathetic outflow.
- 2- A resetting of the baroreflex around a lower homeostatic set point.
- 3- Vascular remodeling may have been reversed over the 24-month period, with that reversal sustained postprocedure.
- Whatever the mechanism, this appears to override any functional reinnervation that may be occurring postprocedure.

# Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial

*Symplicity HTN-2 Investigators**

*Lancet* 2010; 376: 1903–09
Published Online
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DOI:10.1016/S0140-6736(10)62039-9

See Comment page 1878

*Members listed at end of paper

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murray.esler@bakeridi.edu.au

## Summary

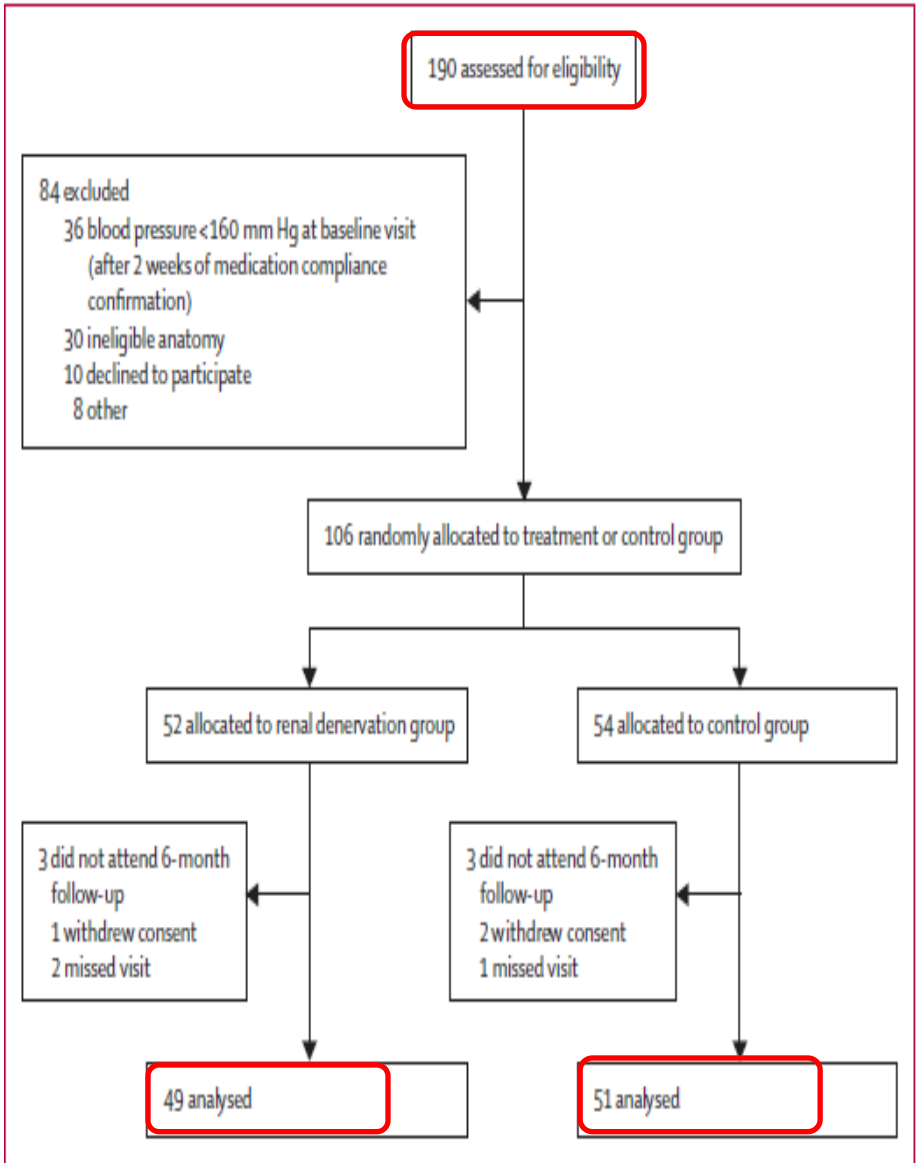
**Background** Activation of renal sympathetic nerves is key to pathogenesis of essential hypertension. We aimed to assess effectiveness and safety of catheter-based renal denervation for reduction of blood pressure in patients with treatment-resistant hypertension.

**Methods** In this multicentre, prospective, randomised trial, patients who had a baseline systolic blood pressure of 160 mm Hg or more (≥150 mm Hg for patients with type 2 diabetes), despite taking three or more antihypertensive drugs, were randomly allocated in a one-to-one ratio to undergo renal denervation with previous treatment or to maintain previous treatment alone (control group) at 24 participating centres. Randomisation was done with sealed envelopes. Data analysers were not masked to treatment assignment. The primary effectiveness endpoint was change in seated office-based measurement of systolic blood pressure at 6 months. Primary analysis included all patients remaining in follow-up at 6 months. This trial is registered with ClinicalTrials.gov, number NCT00888433.

**Findings** 106 (56%) of 190 patients screened for eligibility were randomly allocated to renal denervation (n=52) or control (n=54) groups between June 9, 2009, and Jan 15, 2010. 49 (94%) of 52 patients who underwent renal denervation and 51 (94%) of 54 controls were assessed for the primary endpoint at 6 months. Office-based blood pressure measurements in the renal denervation group reduced by 32/12 mm Hg (SD 23/11, baseline of 178/96 mm Hg, p<0·0001), whereas they did not differ from baseline in the control group (change of 1/0 mm Hg [21/10], baseline of 178/97 mm Hg, p=0·77 systolic and p=0·83 diastolic). Between-group differences in blood pressure at 6 months were 33/11 mm Hg (p<0·0001). At 6 months, 41 (84%) of 49 patients who underwent renal denervation had a reduction in systolic blood pressure of 10 mm Hg or more, compared with 18 (35%) of 51 controls (p<0·0001). We noted no serious procedure-related or device-related complications and occurrence of adverse events did not differ between groups; one patient who had renal denervation had possible progression of an underlying atherosclerotic lesion, but required no treatment.

**Interpretation** Catheter-based renal denervation can safely be used to substantially reduce blood pressure in treatment-resistant hypertensive patients.

# Trial profile



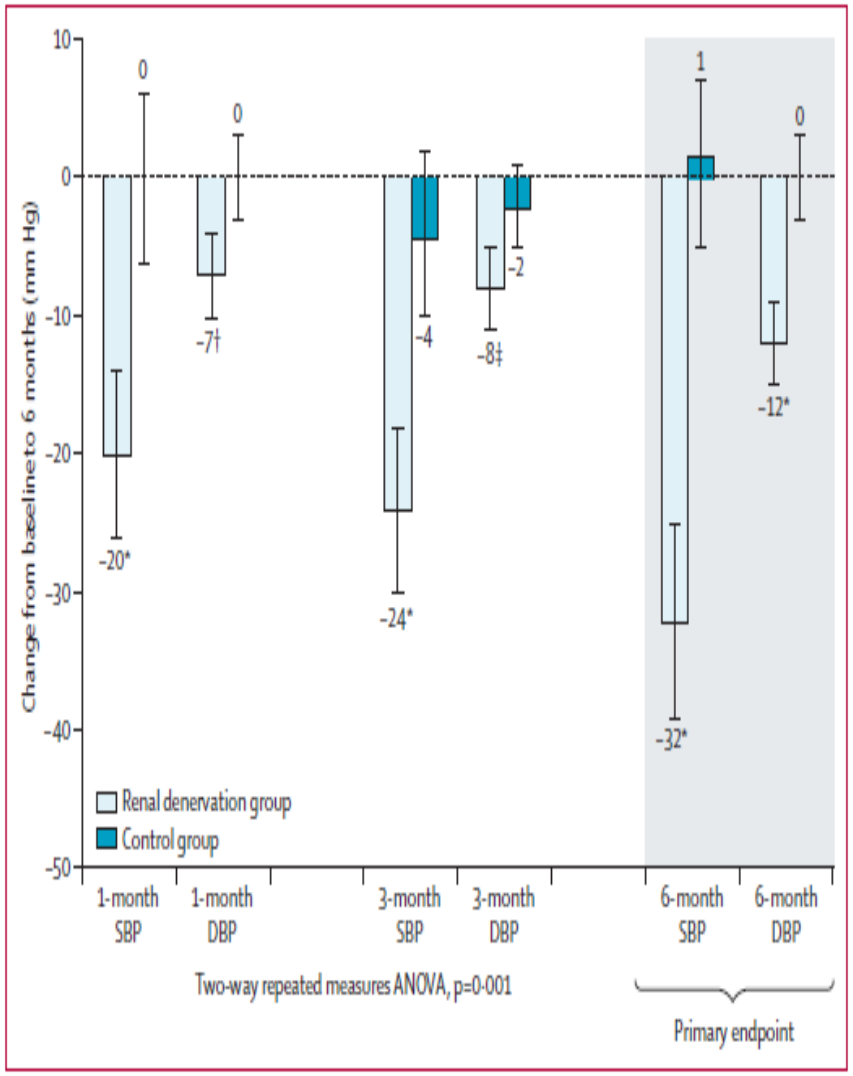

## Baseline clinical characteristics, demographics, and background medications for participants

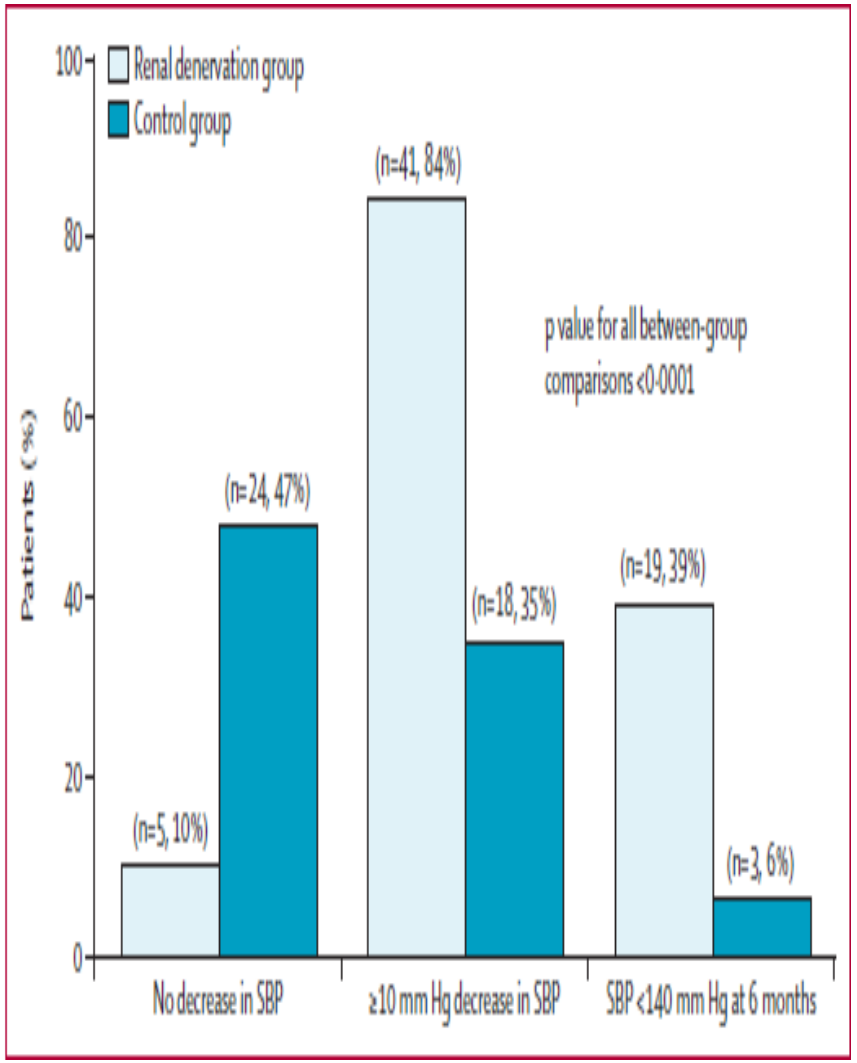
| | Renal denervation group (n=52) | Control group (n=54) |
|---|---|---|
| Baseline systolic blood pressure (mm Hg) | 178 (18) | 178 (16) |
| Baseline diastolic blood pressure (mm Hg) | 97 (16) | 98 (17) |
| Age (years) | 58 (12) | 58 (12) |
| Sex (female) | 18 (35%) | 27 (50%) |
| Race (white) | 51 (98%) | 52 (96%) |
| Body-mass index (kg/m²) | 31 (5) | 31 (5) |
| Type 2 diabetes | 21 (40%) | 15 (28%) |
| Coronary artery disease | 10 (19%) | 4 (7%) |
| Hypercholesterolaemia | 27 (52%) | 28 (52%) |
| eGFR* (mL/min per 1·73 m²) | 77 (19) | 86 (20) |
| eGFR* 45–60 mL/min per 1·73 m² | 11 (21%) | 6 (11%) |
| Serum creatinine (μmol/L) | 91 (25) | 78 (18) |
| Urine albumin-to-creatinine ratio (mg/g)† | 128 (363) | 109 (254) |
| Cystatin C (mg/L)‡ | 0·9 (0·2) | 0·8 (0·2) |
| Heart rate (bpm) | 75 (15) | 71 (15) |
| Number of antihypertension medications | 5·2 (1·5) | 5·3 (1·8) |
| Patients on hypertension medication for more than 5 years | 37 (71%) | 42 (78%) |
| Patients on five or more medications | 35 (67%) | 31 (57%) |
| Patients receiving (drug class) | | |
| ACE inhibitors/ARBs | 50 (96%) | 51 (94%) |
| Direct renin inhibitors | 8 (15%) | 10 (19%) |
| β blockers | 43 (83%) | 37 (69%) |
| Calcium-channel blockers | 41 (79%) | 45 (83%) |
| Diuretics | 46 (89%) | 49 (91%) |
| Aldosterone antagonist | 9 (17%) | 9 (17%) |
| Vasodilators | 8 (15%) | 9 (17%) |
| α-1 blockers | 17 (33%) | 10 (19%) |
| Centrally acting sympatholytics | 27 (52%) | 28 (52%) |

Data are mean (SD) or number (%). eGFR=estimated glomerular filtration rate. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker. *Calculated on the basis of Modification of Diet in Renal Disease Study criteria.[32] †42 participants in the renal denervation group and 43 participants in the control group used for between-group comparisons with the Wilcoxon rank-sum test for two independent samples. ‡39 participants in the renal denervation group and 42 participants in the control group had data for cystatin C available at baseline.

**Renal denervation led to a reduction in blood pressure of 10 mm Hg or more in 84% of treated patients.**

**(office-based measurements )**



# Renal Function

| | Renal denervation group | | Control group | | Difference in mean change (95% CI) | p value |
|---|---|---|---|---|---|---|
| | Patients (n) | Mean change (SD) | Patients (n) | Mean change (SD) | | |
| eGFR* (mL/min per 1·73 m²) | 49 | 0·2 (11) | 51 | 0·9 (12) | -0·7 (-5·4 to 3·9) | 0·76 |
| Serum creatinine (μmol/L) | 49 | 0·2 (17·6) | 51 | -1·1 (10·3) | 1·3 (-4·5 to 7·0) | 0·67 |
| Cystatin C (mg/L) | 37 | 0·1 (0·2) | 40 | 0·0 (0·1) | 0·0 (0·0 to 0·1) | 0·31 |

eGFR=estimated glomerular filtration rate. *Calculated on the basis of Modification of Diet in Renal Disease Study criteria.[17]

*Table 2:* Baseline, change from baseline to 6 months, and difference in change in measured concentrations of eGFR, serum creatinine, and cystatin C for renal denervation and control groups

NO changes in measured renal function with denervation, suggesting that the procedure itself and associated haemodynamic changes have no adverse effects on the kidneys.

# Hypertension treatment for people with resistant hypertension

| Recommendations | Additonal considerations |
|---|---|
| Withdraw any drugs in antihypetensive treatment regimen that have absent or minimal effect | |
| Consider mineralocorticoid receptor antagonists, amiloride, and the alpha-1-blocker doxazosin should be considered (if no contraindication exists) | • *If no contraindications exist* |
| Invasive approaches: renal denervation and baroreceptor stimulation may be considered | • If drug treatment ineffective |
| ***No long-term efficay, safety data for renal denervation, baroreceptor stimulation – only experienced clinicians should use***<br>***Diagnosis and follow-up should be restricted to hypertension Centres*** | |
| Invasive approaches only for truly resistant hypertensive patients | • Clinic values: SBP ≥160 mmHg or DBP ≥110 mmHg with BP elevation confirmed by ABPM |

SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure.

# Conclusion

- **Catheter-based renal denervation, done in a multicentre, randomised trial in patients with treatment-resistant essential hypertension, resulted in significant reductions in BP.**

- **The magnitude of BP reduction can be predicted to affect the development of hypertension-related diseases and mortality.**

- **The technique was applied without major complications.**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# A Controlled Trial of Renal Denervation for Resistant Hypertension

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## ABSTRACT

### BACKGROUND

Prior unblinded studies have suggested that catheter-based renal-artery denervation reduces blood pressure in patients with resistant hypertension.

### METHODS

We designed a prospective, single-blind, randomized, sham-controlled trial. Patients with severe resistant hypertension were randomly assigned in a 2:1 ratio to undergo renal denervation or a sham procedure. Before randomization, patients were receiving a stable antihypertensive regimen involving maximally tolerated doses of at least three drugs, including a diuretic. The primary efficacy end point was the change in office systolic blood pressure at 6 months; a secondary efficacy end point was the change in mean 24-hour ambulatory systolic blood pressure. The primary safety end point was a composite of death, end-stage renal disease, embolic events resulting in end-organ damage, renovascular complications, or hypertensive crisis at 1 month or new renal-artery stenosis of more than 70% at 6 months.

### RESULTS

A total of 535 patients underwent randomization. The mean (±SD) change in systolic blood pressure at 6 months was −14.13±23.93 mm Hg in the denervation group as compared with −11.74±25.94 mm Hg in the sham-procedure group ($P<0.001$ for both comparisons of the change from baseline), for a difference of −2.39 mm Hg (95% confidence interval [CI], −6.89 to 2.12; $P=0.26$ for superiority with a margin of 5 mm Hg). The change in 24-hour ambulatory systolic blood pressure was −6.75±15.11 mm Hg in the denervation group and −4.79±17.25 mm Hg in the sham-procedure group, for a difference of −1.96 mm Hg (95% CI, −4.97 to 1.06; $P=0.98$ for superiority with a margin of 2 mm Hg). There were no significant differences in safety between the two groups.

### CONCLUSIONS

This blinded trial did not show a significant reduction of systolic blood pressure in patients with resistant hypertension 6 months after renal-artery denervation as compared with a sham control. (Funded by Medtronic; SYMPLICITY HTN-3 ClinicalTrials.gov number, NCT01418261.)

**Table 1. Baseline Characteristics of the Study Population.***

| Characteristic | Renal-Denervation Group (N=364) | Sham-Procedure Group (N=171) |
|---|---|---|
| Age — yr | 57.9±10.4 | 56.2±11.2 |
| Male sex — no. (%) | 215 (59.1) | 110 (64.3) |
| Body-mass index† | 34.2±6.5 | 33.9±6.4 |
| Race — no./total no. (%)‡ | | |
| Black | 90/363 (24.8) | 50/171 (29.2) |
| White | 265/363 (73.0) | 119/171 (69.6) |
| Asian | 2/363 (0.6) | 0/171 |
| Other | 6/363 (1.7) | 2/171 (1.2) |
| Medical history — no. (%) | | |
| Renal insufficiency§ | 34 (9.3) | 17 (9.9) |
| Renal-artery stenosis | 5 (1.4) | 4 (2.3) |
| Obstructive sleep apnea | 94 (25.8) | 54 (31.6) |
| Stroke | 29 (8.0) | 19 (11.1) |
| Transient ischemic attack | 28 (7.7) | 13 (7.6) |
| Peripheral artery disease | 19 (5.2) | 5 (2.9) |
| Cardiac disease | | |
| Coronary artery disease | 101 (27.7) | 43 (25.1) |
| Myocardial infarction | 32 (8.8) | 11 (6.4) |
| Diabetes | | |
| Type 1 | 0 | 0 |
| Type 2 | 171 (47.0) | 70 (40.9) |
| Hyperlipidemia — no. (%) | 252 (69.2) | 111 (64.9) |
| Current smoker — no. (%) | 36 (9.9) | 21 (12.3) |
| Family history of hypertension — no./total no. (%) | 305/361 (84.5) | 140/170 (82.4) |
| Hypertension history — no. (%) | | |
| Hospitalization for hypertensive crisis | 83 (22.8) | 38 (22.2) |
| Hospitalization for hypotension | 8 (2.2) | 4 (2.3) |
| No. of antihypertensive medications | 5.1±1.4 | 5.2±1.4 |

**Table 1. (Continued.)**

| Characteristic | Renal-Denervation Group (N=364) | Sham-Procedure Group (N=171) |
|---|---|---|
| Type of antihypertensive medication — no. (%) | | |
| ACE inhibitor | | |
| Patients taking medication | 179 (49.2) | 71 (41.5) |
| Patients taking maximally tolerated dose | 167 (45.9) | 64 (37.4) |
| Angiotensin-receptor blocker | | |
| Patients taking medication | 182 (50.0) | 91 (53.2) |
| Patients taking maximally tolerated dose | 180 (49.5) | 88 (51.5) |
| Aldosterone antagonist | 82 (22.5) | 49 (28.7) |
| Alpha-adrenergic blocker | 40 (11.0) | 23 (13.5) |
| Beta-blocker | 310 (85.2) | 147 (86.0) |
| Calcium-channel blocker | | |
| Patients taking medication | 254 (69.8) | 125 (73.1) |
| Patients taking maximally tolerated dose | 208 (57.1) | 109 (63.7) |
| Centrally acting sympatholytic agent | 179 (49.2) | 75 (43.9) |
| Direct-acting renin inhibitor | 26 (7.1) | 12 (7.0) |
| Direct-acting vasodilator | 134 (36.8) | 77 (45.0) |
| Diuretic | | |
| Patients taking medication | 363 (99.7) | 171 (100) |
| Patients taking maximally tolerated dose | 351 (96.4) | 167 (97.7) |

A total of 1441 patients were assessed for eligibility; of these patients, 535 were enrolled in the trial between October 2011 and May 2013.

# Results

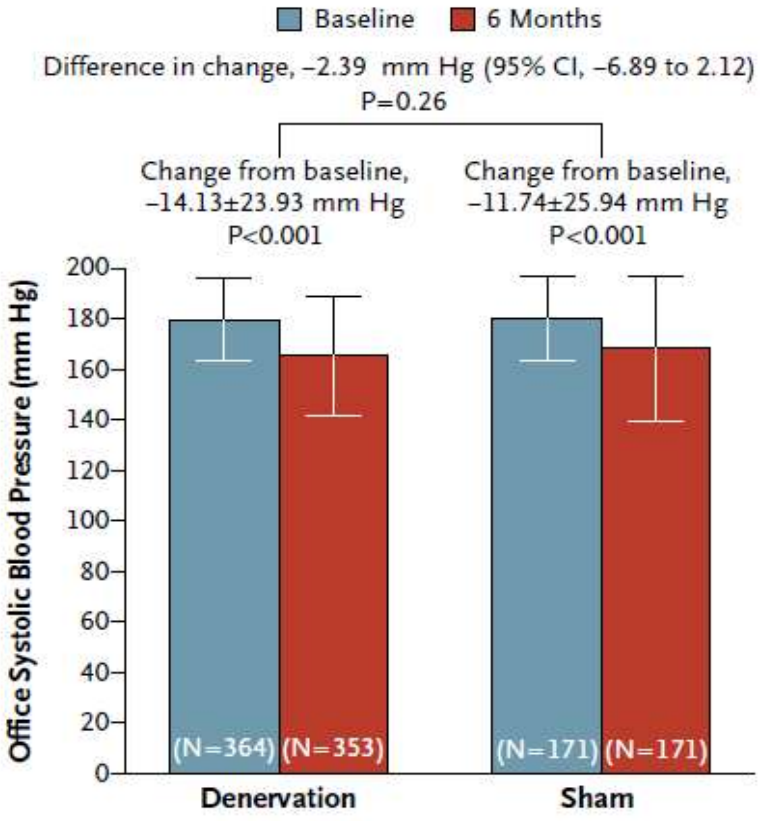



**Figure 1. Primary Efficacy End Point.**

A significant change from baseline to 6 months in office systolic blood pressure was observed in both study groups. The between-group difference (the primary efficacy end point) did not meet a test of superiority with a margin of 5 mm Hg. The I bars indicate standard deviations.

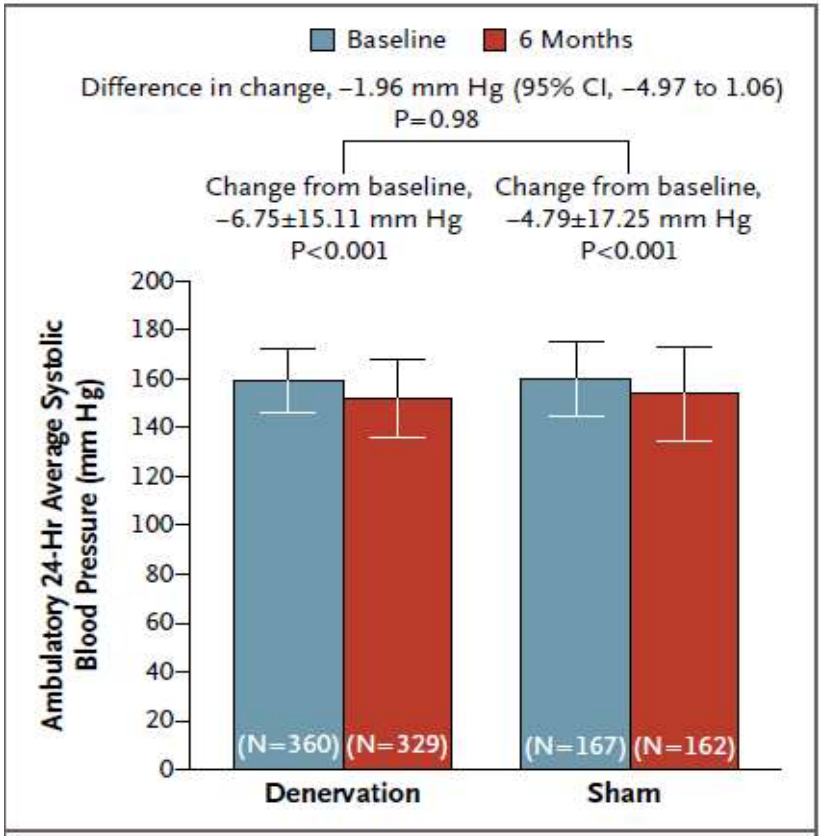



**Figure 2. Secondary Efficacy End Point.**

A significant change from baseline to 6 months in ambulatory 24-hour average systolic blood pressure was observed in both groups. The between-group difference (the secondary efficacy end point for which the study was powered) did not meet a test of superiority with a margin of 2 mm Hg. The I bars indicate standard deviations.

# Primary safety end point

- **There were few major adverse events in the trial: five in the denervation group (1.4%) and one in the sham-procedure group (0.6 ).**

Table 2. Safety End Points.*

| End point | Renal-Denervation Group | Sham-Procedure Group | Percentage-Point Difference (95% CI) |
|---|---|---|---|
| | *no. of patients/total no. (%)* | | |
| Major adverse event† | 5/361 (1.4) | 1/171 (0.6) | 0.8 (−0.9 to 2.5) |
| Composite safety end point at 6 mo‡ | 14/354 (4.0) | 10/171 (5.8) | −1.9 (−6.0 to 2.2) |
| Specific event within 6 mo | | | |
| Death | 2/352 (0.6) | 1/171 (0.6) | 0.0 (−1.4 to 1.4) |
| Myocardial infarction | 6/352 (1.7) | 3/171 (1.8) | 0.0 (−2.4 to 2.3) |
| New-onset end-stage renal disease | 0/352 | 0/171 | — |
| Increase in serum creatinine of >50% from baseline | 5/352 (1.4) | 1/171 (0.6) | 0.8 (−0.8 to 2.5) |
| Embolic event resulting in end-organ damage | 1/352 (0.3) | 0/171 | 0.3 (−0.3 to 0.8) |
| Renal-artery intervention | 0/352 | 0/171 | — |
| Vascular complication requiring treatment | 1/352 (0.3) | 0/171 | 0.3 (−0.3 to 0.8) |
| Hypertensive crisis or emergency | 9/352 (2.6) | 9/171 (5.3) | −2.7 (−6.4 to 1.0) |
| Stroke | 4/352 (1.1) | 2/171 (1.2) | 0.0 (−2.0 to 1.9) |
| Hospitalization for new-onset heart failure | 9/352 (2.6) | 3/171 (1.8) | 0.8 (−1.8 to 3.4) |
| Hospitalization for atrial fibrillation | 5/352 (1.4) | 1/171 (0.6) | 0.8 (−0.8 to 2.5) |
| New renal-artery stenosis of >70% | 1/332 (0.3) | 0/165 | 0.3 (−0.3 to 0.9) |

† The primary safety end point was a composite of major adverse events, defined as death from any cause, end-stage renal disease, an embolic event resulting in end-organ damage, renal-artery or other vascular complications, or hypertensive crisis within 30 days or new renal-artery stenosis of more than 70% within 6 months. The objective performance criteri-

- # Kidney function :
- There were no significant differences between the two groups at any time point
- No significant differences in the subgroup of patients with an estimated glomerular filtration rate of less than 60 ml per minute per 1.73 m2 of body-surface area.

- # Glycated hemoglobin levels :

- There was no significant between-group difference in the change in glycated hemoglobin levels from baseline to 6 months overall.

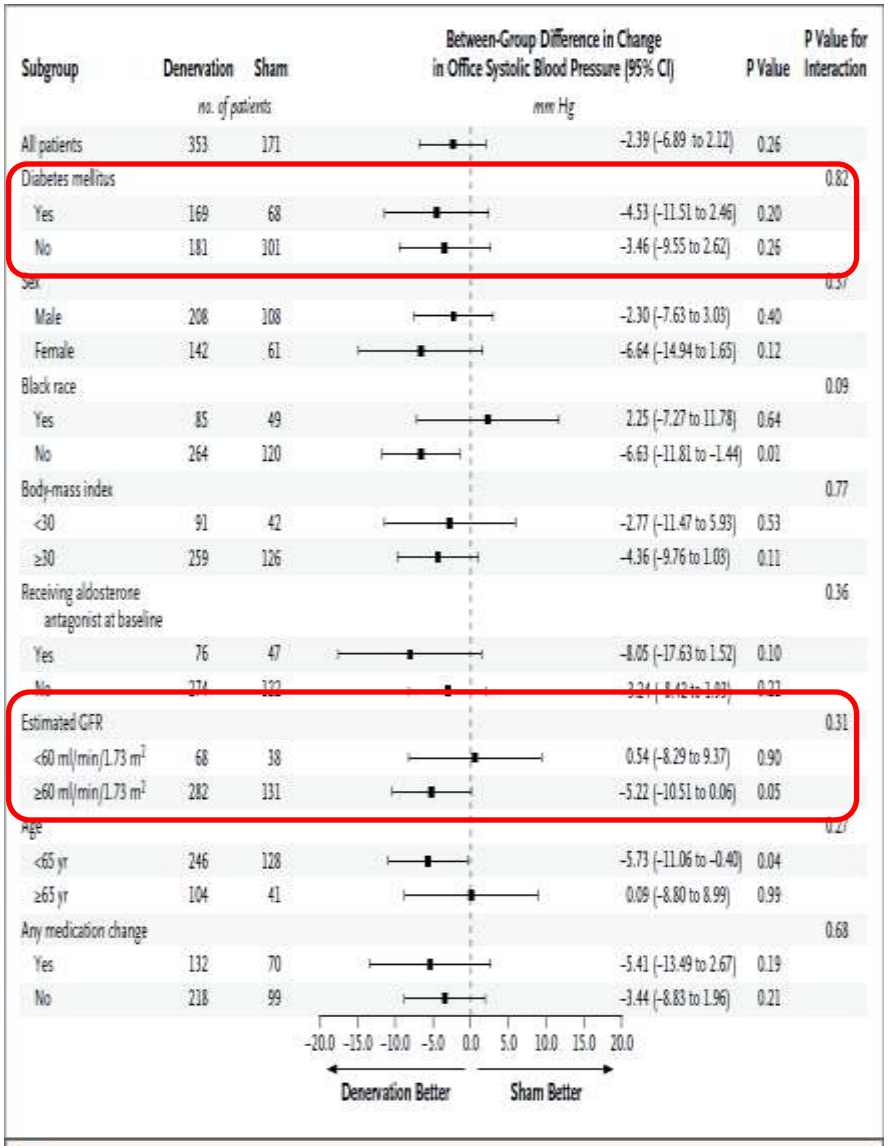



Figure 3. Selected Subgroup Analyses.

Shown are between-group differences in the change in office systolic blood pressure from baseline to 6 months in selected subgroups. The body-mass index is the weight in kilograms divided by the square of the height in meters. GFR denotes glomerular filtration rate.

# Conclusion

- **This randomized, sham-controlled, blinded trial did not show a benefit of renal-artery denervation with respect to either of the efficacy end points for which the study was powered (reduction in office or ambulatory systolic blood pressure at 6 months).**
- **The current trial underscores the importance of conducting blinded trials with sham controls in the evaluation of new medical devices before their clinical adoption.**

# Limitations

- **1- Medication adherence could not be confirmed.**
- **More than 50% of patients with resistant hypertension are known to be nonadherent to medications.**
- **Did not measure urine levels of antihypertensive medications.**

- **2- Follow –up :**
- **The 6-month period from baseline to ascertainment of the primary end point might be too short.**
- **The patients will be followed for up to 5 years.**

- **3- An operator learning curve :**
- **No significant difference was observed in outcomes between operators performing five or more procedures and those performing fewer than five procedures.**
- **No evidencewe found of a learning curve for high-volume operators when earlier procedures were compared with later ones.**

- **4- There was no direct measurement to confirm that the renal nerves were in fact denervated by the procedure, because there is no test that can be easily performed in a large trial.**

- **5- The results of this trial are specific to the catheter tested and cannot necessarily be generalized to other denervation systems**

| | Symplicity 1 | Symplicity 2 | Symplicity 3 |
|---|---|---|---|
| Numbers | 50 | 106 | 535 |
| Controlled | No | Yes | RC Shamed Trial (Patients were unaware of whether they underwent renal-artery denervation or renal angiography only (sham control).) |
| Centers | 5 particpating centers in Australia and Europe | 24 in Europe, Australia, & New Zealand 16 (67%) were hypertension centres of excellence | 88 |
| 1ry outcome | Safety and b.p lowering Office based blood pressure | offi ce-based blood pressure to 6 months after randomisation | office systolic blood pressure from baseline to 6 months |
| 2ry outcome | renal noradrenaline spillover and RF | Acute and chronic procedural safety | the change in mean 24-hour ambulatory systolic blood pressure at 6 months. |
| follow-up | 1 year | 6 months | 6 months |
| Race | Non- white 4% | Non- White 8% | African American 26% |
| Dropout | 80% | | |
| Randomization | | Randomisation; Data analysers were not masked to treatment-group assignment. | 2:1 ratio to undergo renal artery denervation or a sham procedure |

# Questions

- **1) What exactly went wrong for the study SYMPLICITY HTN-3?**
- **2) Is there a need for procedural improvements ?**
- **4) Does renal denervation works ?**
- **3) is it safe ?**
- **3) Is Renal Denervation Dead?**

# What exactly went wrong

- The methodology in this study was far, far, far more rigorous than in previous studies.
- 1- It had a sham control . Patients were blinded to whether they received renal denervation or only renal arteriography.
- They were brought into the catheterization laboratory wearing blindfolds, and headphones with music playing.

2- Blood Pressures monitoring: it prospectively looked at blood pressures not only in the office but also at ambulatory blood pressures.

3- There were mandates for the use of spironolactone.

5- There were anatomic criteria that were not present in other studies.

# What exactly went wrong? Did Race Play a Role

- In the SYMPLICITY HTN-3 trial, 30% of the patients were African Americans. We know that those patients tend to differ in terms of pathophysiology.

- There's evidence indicating that African Americans have a different pathophysiology in different disease states.

- In heart failure, beta-blockers were not as effective in African Americans as in European or Caucasian people.

# What exactly went wrong ?
# Hawthorne effect

- Patients modify their behavior because they are being monitored extensively in a clinical trial, might have led some patients to take their medications more diligently than when on their own.

- **Thought of an interventionalist treating hypertension with a catheter "to a man with a hammer, everything looks like a nail."**

# Need for procedural improvements ?

- There is still a need for procedural improvements.
- Right now, the biggest problem is that it is impossible for clinicians to know if they have achieved successful denervation of the renal artery.
- Number of ablations ? predicted a reduction in systolic blood pressure in the renal denervation group.
- An increasing number of ablations was associated with a consistent and progressive reduction in systolic blood pressure.
- “Circumferentiality" of the renal denervation procedure ?.

# Does renal denervation work ?

- **No question about it.**
- **It wouldn't be around today if it didn't.**
- **It's been studied for over 40 years. It definitely works, but in the absence of anything else !!!!!!!!!!.**

# Is The Renal Denervation Dead?

- **The negative result from Symplicity brings the renal-denervation train to a grinding halt.“**
- **NO, renal denervation is NOT "dead" but rather needs a "reboot," .**
- **Getting back to basics in terms of better understanding the anatomy, neurology, and physiology of the procedure.**
- **leave the door open for renal denervationas it is not just a crack.**



*Expanded results presented at the *American College of Cardiology Annual Meeting 2012* (Krum, H.)

# Is it Safe ?

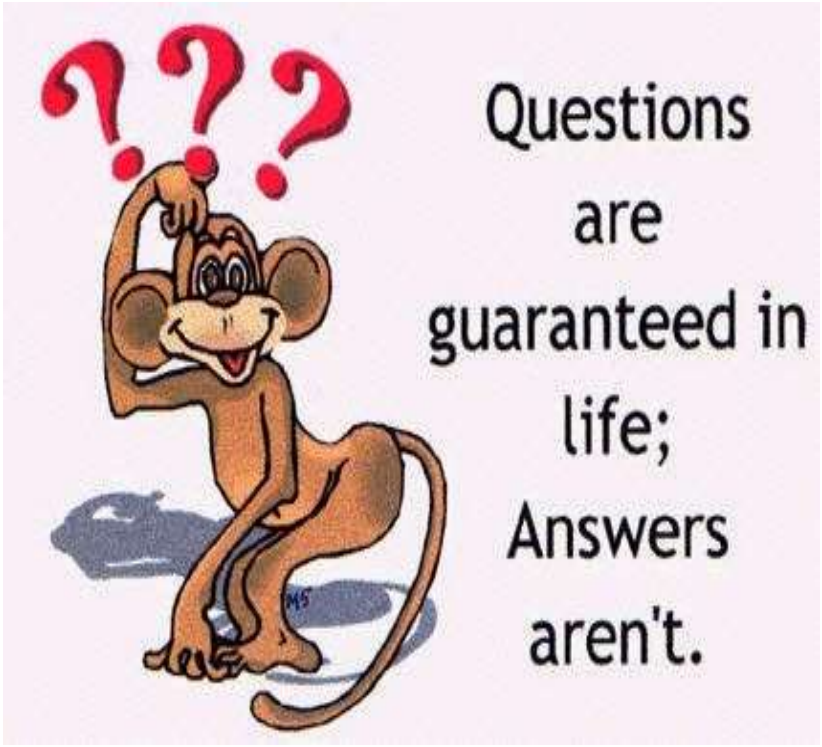
- **Despite the lack of effect on blood pressure in SYMPLICITY HTN-3, there were no safety concerns raised during the trial.**

# Unanswered Questions

1)- Does the decline in GFR continue or flatten?

2)- Will the nephron reinnervate over time?

5)- Did everyone do proper denervation?



Medtronic

# SYMPLICITY HTN U.S. Trial Program


*Caution: Investigational device. Limited by United States law to investigational use.*

## The SYMPLICITY HTN-4 Clinical Trial

The SYMPLICITY HTN-4 clinical trial is very similar to the SYMPLICITY HTN-3 Clinical trial. The purpose of both studies is to provide additional information about a medical device intended to help treat high blood pressure in people whose blood pressure is not controlled despite treatment with multiple blood pressure medications. The primary difference between SYMPLICITY HTN-3 and SYMPLICITY HTN-4 is reflected in the population being studied: SYMPLICITY HTN-3 is investigating the efficacy and safety of renal denervation in volunteers who have an office systolic blood pressure reading above 160 mmHg, whereas SYMPLICITY HTN-4 is investigating the efficacy and safety of renal denervation in volunteers who have an office systolic blood pressure between 140 and 160 mmHg.

| | SYMPLICITY HTN-3 | SYMPLICITY HTN-4 |
|---|---|---|
| Randomized | Yes | Yes |
| Controlled | Yes | Yes |
| Blinded | Yes | Yes |
| [illegible] | [illegible] | [illegible] |
| Number of Centers Participating | Up to 90 in the US | Up to 100 in the US |
| Blood Pressure Required for Inclusion | > 160 mmHg Systolic | 140-160 mmHg Systolic |

If you decide to participate in this study, the potential risks and benefits will be thoroughly explained, and you will have the opportunity to discuss participation both with research staff and your family. If selected, your current blood pressure medications (total daily doses and medication types) will not be changed unless medically necessary. In addition to your current blood pressure medications, you may receive treatment with this investigational therapy.

...

Learn more about this investigational therapy and our clinical trial. To see if you may qualify for this clinical trial, please take this short survey or connect with a participating doctor.

Talk with your doctor about potential risks associated with renal denervation.

Am I a Candidate?

Find a Study Doctor

Important Safety Information

About Medtronic

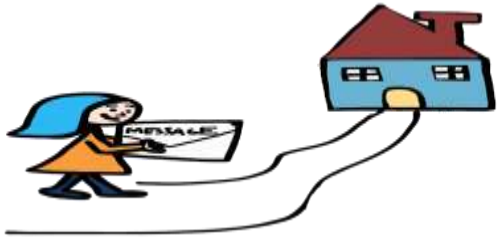
Useful Links

# The Take-Home

- Catheter-based renal denervation in patients with treatment-resistant essential hypertension, resulted in significant reductions in office BP, much less marked when using ABPM.

- The technique was applied without major complications in the shortterm.

- The technique needs still to be evaluated to :
- – Assess its efficacy against the best optimal care using predefined and validated algorhythm of antihypertensive treatments
- – Find out a method indicating the primary success of the denervation
  – Assess its long term safety



# Thank you